Remarks

The foregoing amendments do not require further search or extensive consideration by the Examiner, do not raise new issues, and are believed to place the application in *prima facie* condition for allowance or, at least, present the claims in better form for consideration on appeal. For these reasons, the entry of the requested amendments after final rejection is respectfully requested.

With reference to the Associate Power of Attorney and Change of Address letter filed with applicants' previous response on September 28, 2001, the Examiner is respectfully requested to direct all future communications to the address indicated in that letter and also shown below, to the attention of the undersigned attorney.

It is noted that copies of the references cited in the Information Disclosure Statement mailed on March 8, 2001 were filed and should now be available in the file of copending application Serial No. 09/121,952. The Examiner is respectfully requested to acknowledge consideration of the references.

The Office Action

Applicants are pleased to note the withdrawal of the prior rejection of claims 1-17 and 32-33 under 35 U.S.C. §112, second paragraph, and of the rejection of claims 1-7 under 35 U.S.C. § 102(b) over Wilchek *et al.*

Rejections maintained

(1) Claim 14 remained rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The cancellation of claim 14 moots this rejection. It is emphasized that claim 14 was canceled without prejudice and without acquiescing in its rejection, or any of the positions taken by the Examiner. Applicants' intention is merely to reduce the number of issues in the present case, and to pursue the prosecution of claim 14 in a continuing application.

(2) The various rejections under the judicially created doctrine of obviousness-type double patenting have been maintained. Specifically, claims 1-34 remain rejected over claims 1-37 of copending application no. 09/489,394; and claims 1, 10-12, and 14 remain rejected over claims 1, 5, 6, 7, 19, 26-27 of copending application 09/234,182.

Applicants believe that upon entry of the foregoing amendment, and considering the arguments that follow, the Examiner should find all claims pending allowable. Accordingly, the proper procedure would be to withdraw the obviousness-type double patenting rejections in the present application, and repeat them in the pending application(s), if appropriate.

(3) The rejection of claims 1, 13, 18-22, and 29-31 under 35 U.S.C. 102(e) over Faanes *et al.* (U.S. Patent 5,695,760, filed 4/24/95) has been maintained. Without acquiescing in the rejection, or in the Examiner's reasons for the rejection, claim 1 has been amended to incorporate the subject matter of original claim 5, now canceled. Since claim 5 was not rejected under this section, the withdrawal of the present rejection would be in order.

(4) Claims 1-13, 15-16, 18-24, and 28-34 were rejected under 35 U..C. 103(a) "as being unpatentable" over Faanes *et al., supra.* In justifying the maintenance of the rejection, the Examiner notes that "no scientific evidence is provided to indicate that the Faanes *et al.* conjugates would not work with higher molecular weight PEG, and in fact Faanes *et al.* teaches conjugates with up to 40 kD (see column 12, 62-53)."

It is applicants' position that the Examiner failed to establish a *prima facie* case of obviousness, accordingly, the burden of providing any evidence in rebuttal of the present rejection has not legally shifted to applicants.

In particular, the cited disclosure from Faanes *et al.* concerns a conjugate of a complete antibody (enlimomab) and 5 kD PEG molecules, as opposed to the conjugates of the present invention, which consist of one or more antibody fragments conjugated with PEG molecules. WO Accordingly, the cited disclosure of Faanes *et al.*, even if taken together with the suggestion at col. 12, lines 61-63 that activated PEG molecules of "up to molecular weight 40 kD may . .. be employed," does not teach, or suggest antibody fragment-PEG conjugates with an apparent size of at least 500 kD. Furthermore, Faanes *et al.* has no teaching or suggestion to make conjugates of antibody fragments and PEG molecules, which have both the apparent size specified in claim 1, and the specified ratio between the size of the antibody fragment and the conjugate molecule. Indeed, there is nothing in Faanes *et al.* that would suggest to one of ordinary skill in the art the importance of this ratio. Therefore, Faanes *et al.* provides no motivation to make antibody fragment-PEG conjugates having the characteristics set forth in claim 1, and in the claims dependent therefore. For this reason, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(5) The rejection of claims 1-13, 15-25, and 28-34 under 35 U.S.C. 103(a) "as being unpatentable" over Faanes *et al., supra* and further in view of Zapata *et al.* (FASEB J. 9:A1476, 1995) has been maintained. Zapata *et al.* was cited for its teaching a decrease in clearance with when an antibody fragment (Fab) is conjugated with 10 kD PEG vs. 5 kD PEG. In response to applicants' arguments, the Examiner notes that the reference "does not state a numerical value" for the extent of this decrease.

The numerical value is from the poster presentation corresponding to the Zapata et al. Abstract, a copy of which was filed as Reference #108 in connection with copending application Serial No. 09/121,952. In discussing the results of pharmacokinetic analysis, the poster states that "[s]erum clearance decreased approximately 3- and 6-fold from 189 mL/hr/kg for the original Fab to 66 and 31 mL/hr/kg for the Fab-SH-PEG 6,000 and Fab-SH-PEG 10,000 constructs respectively." In the "Conclusion" section, the authors state that the "nonspecific clearance of an Fab with a MW of 49 [should be 48] KDa can be decreased as much as 6-fold by the addition of a 10,000 PEG moiety." This is the disclosure applicants relied on in their previous response, and the same argument is maintained and repeated here.

While Zapata *et al.* suggests that decrease in serum clearance can be obtained by increasing the molecular weight of the PEG moiety in their conjugates, it has no teaching or suggestion that the ratio of the molecular weight of the antibody fragment to that of the antibody fragment-PEG conjugate would be important, and should be kept within certain limits.

Accordingly, the combination of Faanes *et al.* and Zapata *et al.* does not make obvious the claims rejected and the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(6) The rejection of claims 1 and 33-34 under 35 U.S.C. § 103(a) over Faanes *et al., supra*, and further in view of Harlow *et al.* has been maintained from the previous Office Action. The Farlow *et al.* patent has been discussed above. Applicants have shown that Faanes *et al.* does not make obvious the conjugates claimed in claim 1. There is nothing in Harlow *et al.* that would supply the teaching missing from Faanes *et al.* Therefore, the present rejection should be withdrawn.

(7) The rejection of claims 1, 26 and 27 under 35 U.S.C. § 103(a) over Faanes *et al., supra*, and further in view of Doerschuk *et al.* has been maintained from the previous Office Action. The Farlow *et al.* patent has been discussed above. Applicants have shown that Faanes

et al. does not make obvious the conjugates claimed in claim 1. There is nothing in Doerschuk *et al.* that would supply the teaching missing from Faanes *et al.* Therefore, the present rejection should be withdrawn.

The present Amendment and Response is accompanied by a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 11, 2002

By: _____

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Version with markings to show changes made

In the Claims:

Claims 5 and 14 were canceled, without prejudice.

Claims 1 and 6 were amended as follows:

1. (Amended) A conjugate consisting essentially of one or more antibody fragments covalently attached to one or more nonproteinaceous molecules, wherein the apparent size of the conjugate is (a) at least about 500 kD, and (b) at least 8 fold greater than the apparent size of the antibody fragment.

6. (Amended) The conjugate of claim [5] 1, wherein the apparent size of the conjugate is at least 15 fold greater than the apparent size of the antibody fragment.

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